Figure 2-20-M-4 MOU Between the Department of VA Medical Center Tampa, Florida & DoD (Continued)

3. For individuals with TBI with dual VA and TRICARE/CHAMPUS eligibility, VAMC shall be responsible for all care of such patients listed below under the DVHIP Protocol II. The VAMC shall ensure that the care provided to the patients with dual eligibility listed below under the DVHIP is not billed to the DoD demonstration claims processor. With regard to the patients with dual VA and TRICARE/CHAMPUS eligibility, VAMC shall be responsible for the following beneficiary care under the DVHIP until the enrollment system required by Public Law 104-262 is fully implemented:

a. care for mandatory/non-discretionary veterans
b. care for veterans for service-connected conditions

Upon implementation of that enrollment system, the VAMC shall be responsible for veterans who are enrolled or who may be provided care from VA because they are exempt from enrollment.

4. For individuals without VA eligibility who appear to meet the inclusion criteria in the DVHIP Protocol II, VAMC shall refer such patients to the DoD demonstration claims processor, namely, Palmetto Government Benefits Administrators (PGBA), for TRICARE/CHAMPUS eligibility verification on the Defense Enrollment Eligibility Reporting System (DEERS). The toll free telephone number for PGBA is 1-800-779-3060 and the address is:

PGBA
DVHIP Demonstration Project
P.O. Box 100514
Florence, SC 29501-0514

Upon receipt of a written/faxed TRICARE/CHAMPUS eligibility verification of a beneficiary from PGBA, VAMC shall furnish inpatient services to the beneficiary in accordance with the DVHIP Protocol II.

5. Participating VAMC shall be responsible for obtaining information regarding possible third party liability and other health insurance (OHI) coverage of the TRICARE/CHAMPUS beneficiary.

(1) The VAMC shall collect from the third party or the OHI in accordance with VA procedures and bill any remaining balance of the total per diem amount to the demonstration claims processor within thirty (30) days of the receipt of the payment from the OHI. The VAMC shall ensure proper entry regarding the OHI on the

Figure 2-20-M-4 MOU Between the Department of VA Medical Center Tampa, Florida & DoD (Continued)

UB-92 claim form before submitting the claim form to the demonstration claims processor.

(2) In the event that the VAMC is unable to collect from a third party or the OHI for health care services that would be covered under the third party liability or by the OHI if provided by a private provider, no bill shall be presented by the VAMC to the demonstration claims processor.

6. The VAMC shall submit claims for TRICARE/CHAMPUS-eligible patients for inpatient care under the DVHIP Protocol II based on the per diem rate (paragraph 2) on a UB-92 claim form to the DoD demonstration claims processor at the address provided in paragraph 4, above. The DoD agrees to waive the billing itemization requirements.

7. For a TRICARE/CHAMPUS-eligible patient, the VAMC shall submit one claim for billing for the initial inpatient evaluation, rehabilitation care, and the initial post-discharge evaluation within thirty (30) calendar days upon completion of the initial post-discharge evaluation. Claims for admissions at 6-, 12-, and 24-month follow-ups shall be submitted by VAMC within thirty (30) calendar days of completion of each follow-up evaluation. In a case where care of a TRICARE/CHAMPUS-eligible patient is terminated during or after the initial inpatient evaluation or prior to completion of the treatment under the DVHIP Protocol II, the VAMC shall submit the claim within thirty (30) calendar days of such termination.

8. The VAMC shall appoint a social worker/case manager to assist the TRICARE/CHAMPUS beneficiaries in placement following discharge to ensure they receive the full benefit of any available health care entitlements.

9. In the event that a TRICARE/CHAMPUS-eligible patient receives care from the VAMC and the care is determined not to be authorized under the DVHIP Protocol II, the VAMC shall hold the TRICARE/CHAMPUS-eligible patient harmless for any cost of the care.

10. The VAMC and the DoD demonstration claims processor (paragraph 4) shall establish points of contact who shall be familiar with this MOU and the TRICARE/CHAMPUS instructions regarding the DVHIP demonstration project. The points of contact shall assist in resolving claims, billings, DEERS eligibility verification, and other related issues as they arise.

11. Unless otherwise agreed between the VAMC and TRICARE Support Office/OCHAMPUS, the VAMC shall provide coordination support on any billing and

Figure 2-20-M-4 MOU Between the Department of VA Medical Center Tampa, Florida & DoD (Continued)

demonstration related issues for up to 12 months after termination of the demonstration. Unless otherwise directed by TRICARE Support Office/OCHAMPUS, the DoD claims processor shall provide the claims processing support for up to 12 months after termination of the demonstration.

IV. ADMINISTRATIVE AND CLINICAL RESPONSIBILITIES

The Assistant Secretary of Defense for Health Affairs, in consultation with the Under Secretary for Health of the Department of Veterans Affairs, shall conduct overall program management relating to this MOU and the DVHIP.

V. ISSUE RESOLUTION

Throughout the course of this agreement, issues involving interpretation of its provisions, unanticipated technical matters, and proposed modifications in the interest of equity can be expected. The Departments agree to work together in a collegial manner and in good faith to resolve such issues in a manner that is fair, equitable, supportive of the objectives of the pertinent laws, and responsive to the needs of VA and DoD beneficiaries.

VI. POINTS OF CONTACT

a. For the Department of Veterans Affairs:

Arthur S. Hamerschlag
Director, Medical Sharing Office (166)
Department of Veterans Affairs
Washington, DC 20420
(202) 273-8403

Steven Scott, M.D.
Local Principal Investigator
VA Medical Center
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(813) 972-7506

b. For the Department of Defense:

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Director, Clinical Consultation
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Washington, DC 20301-1200
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Walter Reed Army Medical Center
Washington, DC 20307
(202) 782-6345

Figure 2-20-M-4 MOU Between the Department of VA Medical Center Tampa, Florida & DoD (Continued)

VII. MODIFICATION OR TERMINATION

a. Either the VA or DoD may propose amendments modifying this agreement at any time. Before any amendment shall become effective, both parties must agree in writing to the modification. The effective date of any amendments shall be the date agreed upon and specified in the agreement, or, if no date is specified, the last date upon which representative officials of both parties have agreed in writing to the amendment.

b. This MOU terminates (1) upon completion of the DVHIP Protocol II study which is projected to last for three years, or (2) may be terminated at any date upon 60 days notice in writing to the other party.

VIII. EFFECTIVE DATE

August 1, 1997.

Figure 2-20-M-4 MOU Between the Department of VA Medical Center Tampa, Florida & DoD (Continued)

Richard A. Silver
Director
VA Medical Center
Tampa, Florida

Date 6-10-96

Kenneth W. Kizer, M.D., M.P.H.
Under Secretary for Health
Department of Veterans Affairs

Date 05/23/97

Edward D. Martin, M.D.
Acting Assistant Secretary of Defense
for Health Affairs

Date JUN 20 1997

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II

(This is an attachment to each MOU.)

DEFENSE AND VETERANS HEAD INJURY PROGRAM (DVHIP)

PROTOCOL II

TRAUMATIC BRAIN INJURY REHABILITATION:

A CONTROLLED, RANDOMIZED MULTICENTER STUDY OF TWO

INTERDISCIPLINARY PROGRAMS WITH ADJUVANT PHARMACOTHERAPY

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Richard A. Lanham, Jr., Ph.D., Minneapolis VAMC
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Glenn Curtiss, Ph.D., Tampa VAMC
Alexander K. Ommaya, M.A., DVHIP
Deana Haggerty, M.S., Richmond VAMC
Valarie Burgess, M.S., CCC-SLP, Richmond VAMC
and the DVHIP Study Group

December 23, 1994

Attachment to MOU

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

PROBLEM TO BE INVESTIGATED

Traumatic brain injury (TBI) is the principal cause of death and disability in Americans under age 35, with consequences ranging from physical to long-term cognitive, behavioral, and social deficits. Total cost in the United States is conservatively estimated at $39 billion per year. Survivors of TBI tend to manifest specific patterns of impairment, which distinguish them from stroke or other neurologically impaired patients. While there is general consensus that some level of TBI-specific rehabilitation is beneficial, the exact nature and timing of the rehabilitation elements which are best for a given patient remain highly controversial. Most rehabilitation strategies, although often very expensive, have not been subjected to the degree of scientific scrutiny for effectiveness and cost efficiency which has been expected of other medical therapies.

HYPOTHESES

1. In moderate to severe TBI survivors, a comprehensive postacute rehabilitation program focusing on specific impaired cognitive processes will differ by at least 15% in ultimate patient functional outcome from one with a more functional orientation.
2. Such a cognitive rehabilitation program will improve performance on measures of specific cognitive abilities when compared to a more functional orientation.
3. Patients who receive sertraline in combination with their rehabilitation will have significantly better outcome than those who receive placebo.
4. Exploratory Hypotheses
   a. Apathetic, nondepressed TBI survivors who receive the stimulant methylphenidate in combination with their rehabilitation will have better outcome than those who receive placebo.
   b. Specific subsets of TBI patients (i.e., depressed or agitated patients) will receive more benefit from sertraline than those without depression or agitation.
   c. Specific subsets of TBI patients will receive more benefit than others from either cognitive or functional therapy.

OBJECTIVES

1. To evaluate the effectiveness and relative cost efficiency of two alternative TBI rehabilitation strategies.
2. To evaluate the effectiveness of sertraline as an adjuvant to two alternative TBI rehabilitation strategies.
3. To further develop and validate outcome measures which define the short-term and long-term neurologic, cognitive, behavioral, and psychosocial consequences of moderate to severe TBI.

MEDICAL APPLICATION

The military loses thousands of man-years in experience and hundreds of thousands of training and education dollars each year due to effects of traumatic brain injuries in soldiers prematurely returned to active duty or separated outright. Many young adults never return to premorbid skills or responsibilities after TBI, despite intensive and comprehensive rehabilitation efforts on their behalf. On the other hand, many others with similar injuries successfully return to active lives, if not premorbid levels, with little or no systematic rehabilitation. TBI rehabilitation is labor intensive, expensive, and emotionally demanding of patient and staff alike. A major long-term goal of this program will be to determine the effectiveness and relative cost efficiency of alternative TBI rehabilitation strategies and to define optimal care for survivors of TBI.

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

Background/Status

There is about one TBI hospitalization per minute in the USA, at an estimated overall cost of some $39 billion per year.[1,2] Similarly, TBI accounts for over 40% of fatalities and at least 14% of surviving casualties in combat and for a disproportionate amount of acute and long-term combat casualty care resources. In peacetime, there are over 8,000 TBI hospitalizations in Department of Defense (DoD) and Department of Veterans Affairs (DVA) hospitals each year. These peacetime injuries are similar in nature and cause to those occurring in the general civilian population. Over the past two decades, we have come to recognize that it is usually inappropriate and counterproductive to lump the postacute management of TBI with that of other neurologic disabilities, and that most TBI patients would benefit from at least some level of specialized, interdisciplinary rehabilitation. In that time, there has been a rapid growth of mostly private and often very expensive TBI rehabilitation programs throughout the nation. These have filled a vacuum in TBI care, but the exact form and intensity of TBI rehabilitation required for a given patient remains highly controversial. Few, if any, programs or program elements have been subjected to the degree of scientific scrutiny for efficacy and cost efficiency that is usually applied to other medical treatments. In particular, the remarkable ability of the young adult brain to compensate for injury naturally has often not been considered in the evaluation of outcome from various treatments. For example, over 55% of moderate to severe head injured Vietnam veterans were gainfully employed some 15 years postinjury with no formal TBI rehabilitation.[3]

The relative paucity of scientific program evaluation has in turn made it difficult to focus rehabilitation efforts on those elements most likely to return the patient to independent living and/or gainful employment. Some institutional programs may even be counterproductive, particularly if they inadvertently foster continued dependence in the patient.

Concepts regarding the ideal form for a TBI rehabilitation program are rapidly changing. Functional areas which usually are addressed in comprehensive rehabilitation programs include: mobility, activities of daily living, speech, language and communication, cognitive or mental processes, and behavior and social interaction. Depending on the focus of the program, certain areas may be emphasized or de-emphasized in any given program. While there tends to be reasonable consensus in approaches to the rehabilitation of mobility and activities of daily living, wide variability exists in the rehabilitation of communication, cognitive processes, behavior and social interaction and work skills.

At least three alternative, yet overlapping, TBI rehabilitation strategies have evolved, all of which attend to basic mobility, activities of daily living, and traditionally recognized speech and language deficits in a similar manner. The first, and perhaps most widespread, strategy seeks to identify and target further specific cognitive, behavioral, communication, or other deficits for individual therapy.[4,5,6,7] Such programs generally involve interdisciplinary evaluation and intensive individual or small group intervention in an inpatient therapeutic setting. The second approach does not emphasize targeting of such specific deficits, but assumes that most functional impairments will improve as the patient is provided the opportunity to practice appropriate function in a supportive rehabilitation environment. The third strategy involves the use of adjuvant psychotropic medications to improve performance during the rehabilitation process and beyond.

Cognitive Rehabilitation

Cognitive rehabilitation of TBI survivors is one of the more controversial elements of the first approach. The underlying assumption is that cognitive and behavioral deficits are the basic cause of the ultimate psychosocial dysfunction, and their rehabilitation will result in cognitive reorganization with a generalized improvement in overall function. At least four basic subareas can be defined within the concept of *"cognitive rehabilitation"* for TBI. These are: (1) memory, (2) executive functions, (3) attention, and (4) pragmatic communication. Prospective memory is the ability to learn information, retain it across time, and retrieve it at the appropriate time, while working memory is a subsystem for temporary storage and manipulation of information. Executive functions include self-awareness, self-cueing, reasoning, and problem-solving skills, and the ability to monitor and control one's performance. Attention processes include the ability to focus attention, to shift and/or divide

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

attention, and to sustain attention on a selected stimulus. Pragmatic communication refers to those behaviors which have the potential, if used inappropriately, to disrupt or penalize conversational interchanges. Such impairments may or may not include traditionally recognized speech and language deficits, and are often seen after TBI. Pragmatics includes interactive behaviors such as initiation of conversation, topic management, turn taking, modulation of voice volume and prosody, verbal organization, and active listening.

These four cognitive elements obviously interact. For example, attention is strongly associated with the current concept of working memory[8] in which a central *"memory executive"* allows for temporary storage of information while attention is shifted to other tasks. Thus, while cognitive rehabilitation can be divided into various elements, they should all be considered part of an interdependent system.

We have built therapeutic modules around each of these four basic elements, and within each module; tasks are arranged hierarchically from simple to complex, depending on the Rancho Los Amigos cognitive level of a given patient. (Appendix A) For example, intervention for lower level patients would be centered on environmental modification, while higher level patients would undergo training of specific skills and/or remediation of underlying cognitive deficits. In addition, basic occupational, physical, and speech therapies will be utilized as needed to treat specific inpairments.

Functional TBI Rehabilitation

The second approach is more empirical, also utilizing basic occupational therapy (OT), physical therapy (PT), and speech therapies as needed, but focusing on overall functional outcome.[9] It generally assumes that specific physical, cognitive, speech, and behavioral impairments will recover better when practiced in a therapeutic setting representative of the social environment to which the patient will return. It relies on traditional physical, occupational, and speech therapies supplemented by recreational and group therapies. Such functional programs tend to be less labor intensive, and thus initially less expensive than cognitive therapies. This approach reflects current practice at various facilities around the country, and thus reflects a more traditional approach to inpatient TBI rehabilitation.

Prior to the development of *"cognitive remediation"*, and despite methodological difficulties, uncontrolled studies first indicated that a interdisciplinary inpatient rehabilitation approach seemed to improve outcome in these patients,[10,11,12,13] and that patients with severe head injuries benefited more from early versus late inpatient rehabilitation. Only one study has compared brain-injured patients who underwent rehabilitation to patients who did not, but interpretation of results was complicated by differing injury severity in the two groups. After correcting for this difference, the authors suggested a possible benefit of general rehabilitation.[14] Inpatient rehabilitation in this study included *"cognitive therapy"*, but the nature or extent of this therapy was not described. It is doubtful that it was similar to current notions of cognitive remediation because the study sample was collected in 1977 and 1979, when cognitive remediation was in the early stages of development.

We have surveyed directors, case managers, and therapists from various brain injury programs and discovered a high degree of uniformity between sites in the amount and types of therapies offered. All sites surveyed easily surpassed the minimum requirements of JCAHO, which state that a *"comprehensive physical rehabilitation program or unit directly provides, at a minimum: rehabilitation medicine, rehabilitation nursing, social work, occupational therapy, physical therapy, and speech-language pathology services"*.[15] Other services, such as recreational therapy, neuropsychological rehabilitation, prosthetics, and vocational rehabilitation may be offered, but are not considered necessary for accreditation.

The details of what therapists actually do are more difficult to establish, but based on responses to our questionnaire, this also appeared to be relatively uniform. However, much of what therapists do with patients is still intuitive, supportive, and a reflection of their own style and experience. For example, therapists from several disciplines used selected *"cognitive"* interventions routinely in their clinical practice. While for practical reasons it may thus be impossible at present to eliminate all variability between individual therapists, certain therapeutic guidelines will be necessary across centers in order

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

to ensure comparability of results and the ultimate validity of the study. Specifically, these guidelines will include isolation and restriction of cognitive rehabilitation training from the functional program patients without eliminating use of certain less specific, commonly accepted and routinely utilized cognitive rehabilitation techniques, such as memory books or helping patients learn to self-monitor and redirect cognitive processes. In addition, the total hours of therapy per week provided by a given discipline will be kept comparable within a specified range for each of the treatment arms (see Conduct of Study and Appendices below).

Pharmacological Therapies

Finally, a growing body of basic, as well as clinical, literature suggests that adjunctive pharmacological treatment will not only facilitate behavioral management during rehabilitation therapy, but may result in a better ultimate functional outcome. The basic premise is that TBI results in damage to adrenergic, dopaminergic, and/or serotonergic pathways and that such damage is in turn responsible for attention, motivation and other behavioral deficits. Use of adrenergic (dextroamphetamine, methylphenidate), dopaminergic (bromocriptine, amantadine), or serotonergic (buspirone, fluoxetine, sertraline) agonists has thus been variously proposed in TBI. The basic animal work of Feeney and colleagues has further supported the notion that combined use of such stimulants, plus rehabilitation, improves ultimate recovery.[16] Clinical support for the use of noradrenergic agonists to improve attention, concentration and behavioral measures derives from the experience with attention deficit disorder (ADD).[17] Single case design and placebo controlled TBI series have reported improved cognitive performance[18] or decreased anger[19] with methylphenidate and/or dextroamphetamine.[20] However, there is no clear persistent benefit with these drugs, and results remain mixed even though both have been in use for years in TBI patients. Their use appears most justified in sleepy or apathetic patients.

Interest in serotonergic drugs has been aroused by their usefulness in depression, as well as by the discovery of low CSF levels of the serotonin metabolite, 5-HIAA, in violent, impulsive patients[21] and in TBI patients with frontotemporal lesions. Thus, the combination of irritability, impulsivity, and decreased mood and motivation so commonly seen after TBI has been linked most closely to the serotonin system. In addition, serotonin's metabolite melatonin regulates circadian sleep rhythms which are commonly affected after TBI. Preliminary clinical studies with buspirone,[22] amytryptiline,[23] fluoxetine,[24] and sertraline[25,26] also support the use of serotonin agonists in TBI. Sertraline has been selected for this study as the safest, easiest to administer (once daily), most specific, and theoretically most promising of the neurotransmitter agonists available for TBI. The increased rate of organic depression often seen after TBI is further rationale for the use of a drug such as sertraline. However, there remains some controversy regarding the use of SSRIs in nondepressed, apathetic patients. In such patients, methylphenidate may be a preferable choice.[27]

In summary, all three rehabilitation strategies have been reported to increase the functional and independent living skills of TBI survivors, and decrease common neurobehavioral sequelae, such as cognitive slowing, mental inflexibility, impulsivity, and impoverished social skills. Several studies have reported that comprehensive brain injury rehabilitation speeds return to work after TBI, and increases patients' abilities to resume previous levels of vocational independence. In general, however, TBI rehabilitation outcome studies have been poorly controlled, if at all. Criticisms include their (1) lack of standardized interventions within or across settings; (2) unspecified, or unstandardized patient inclusion criteria; (3) lack of random assignment of patients to treatment conditions; (4) lack of meaningful, consistent, or focused outcome criteria; and (5) lack of standardized evaluation.[28,29,30,31] As a result, the question remains as to whether and which interdisciplinary TBI rehabilitation approach is the most effective and cost efficient method of returning traumatic brain injured persons to maximum potential levels of community or vocational integration.

These questions are unlikely to be satisfactorily resolved other than by prospective, randomized, controlled clinical studies. The DoD and DVA health care systems offer a unique peacetime setting in which to address this national problem. Their populations are relatively uniform (young, healthy and

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

employed preinjury); and use of their existing facilities and medical networks will not only decrease costs considerably, but will allow for the standardization that is essential for proper multicenter studies.

The Defense and Veterans Head Injury Program (DVHIP) was established in response to a direct appropriation in the DoD Health Budget for FY92, in order to find solutions to the problem of TBI in the military and DVA; but the broader objective is to find solutions which are relevant to the national problem as well. At present the DVHIP includes eight regional military and DVA TBI centers, and a central office at the Uniformed Services University of the Health Sciences (USUHS) coordinating patient tracking, study design, data collection, and analysis. Another fundamental element of the program is a close collaboration with the National Head Injury Foundation's (NHIF) educational, family, and community integration activities. The present treatment protocol is one of the major controlled rehabilitation trials for TBI survivors to be undertaken by the DVHIP over the next several years.

STUDY DESIGN AND CONDUCT

All eligible patients will be randomized to one of four treatment groups. A factorial experimental design will be utilized in order to test simultaneously for the effects of rehabilitation approach and drug upon outcome in TBI patients. This design will permit us to evaluate the separate effects of treatment approach, drug, and their interactions. We hypothesize that the benefits of adjunctive drug therapy may be more pronounced in one rehabilitation approach than in the other.

Moderate to severe TBI patients will be randomized to a two ±1 month comprehensive rehabilitation program emphasizing individual cognitive therapies, or to a more functional interdisciplinary rehabilitation program utilizing standard physical/occupational and speech therapies supplemented by recreational and group therapies. Patients will be simultaneously randomized to receive active drug or placebo during their respective inpatient program. The drug aspect of the protocol will be double-blinded and placebo controlled. After discharge, all patients will be referred to a facility near their home with specific recommendations for continued follow-up based on their residual level of disability. All of these programs will exceed the current Standard of Care (SOC) for most service members who have experienced recent head injury. Primary outcome measures will include functional independence and return to work/school, as well as specific quality of life, neurologic, neuropsychologic, EEG, and behavioral test variables.

PATIENTS

Inclusion Criteria

1. Moderate to severe closed head injury, manifested by admission GCS <12, PTA >24 hours, or focal cerebral contusion on CT/MRI or Loss of Consciousness (LOC), >12 hours.
2. Within three months of injury at randomization.
3. Rancho Los Amigos cognitive level of 5-7 at randomization.
4. Volunteer informed consent signed by patient or family.
5. Military or veterans health care beneficiary.
6. Age 17-55.

Exclusion Criteria

1. Unwillingness to participate in rehabilitation program or cooperate with investigators.
2. History of prior severe traumatic brain injury or other severe neurologic or psychiatric condition, such as psychosis, stroke, multiple sclerosis, or spinal cord injury.

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

3. Any contraindication to the use of sertraline, or for apathetic patients, contraindications to the use of methylphenidate.

Given the coincidence of alcohol abuse and TBI exceeding 50% in some studies, alcohol or drug abusing subjects will not be excluded from the present protocol, but will be referred for substance abuse intervention in conjunction with their participation in this study. In addition, the randomization procedure will be monitored to ensure an even distribution of substance abuse patients to the treatment arms.

Similarly, it is likely that some patients will have received some formal rehabilitation prior to referral into this protocol. While it is not feasible to exclude such patients from specialized protocol treatment at this time, all such prior therapy will be recorded for subsequent analysis, and every attempt will be made to randomize patients early in their recovery course and before participation in extensive TBI rehabilitation programs elsewhere.

CONDUCT OF THE STUDY

Subjects will be admitted to one of four participating centers, where they will undergo a comprehensive standardized evaluation including neurologic, neuropsychologic, psychiatric, MRI, EEG, and psychosocial testing, and a functional PM&R assessment of adaptive skills. This initial testing will include two administrations, at least five days apart of the modified Marin Apathy Scale (Appendix C). Nondepressed apathetic patients (Marin score < 12) will be placed in group *"M"* (methylphenidate) for purposes of drug treatment randomization. All other patients will be in drug group *"S"* (sertraline). A diagnosis of depression for these purposes will be based on the formal psychiatric evaluation, including the Hamilton Depression Rating Scale and the Present State Examination.

Randomization

Following the comprehensive evaluation, nonapathetic patients (group *"S"*) will be randomly assigned to one of four groups:

Group A-1: Two months (± 1 month) of treatment in Rehabilitation Program A (focus on individual cognitive rehabilitation, Appendix A), with adjunct sertraline, 100 mg daily for six months.

Group A-2: Two months (± 1 month) of treatment in Rehabilitation Program A, with adjunct placebo for six months.

Group B-1: Two months (± 1 month) of treatment in Rehabilitation Program B (focus on functional rehabilitation, Appendix B), with adjunct sertraline, 100 mg daily for six months as below.

Group B-2: Two months (± 1 month) of treatment in Rehabilitation Program B, with adjunct placebo for six months.

Similarly, in addition to being randomized into the cognitive or functional Rehabilitation Program, nondepressed apathetic patients (group *"M"*) will also be randomized to receive either methylphenidate, 10 mg, or placebo, b.i.d. for the duration of their inhospital rehabilitation.

A patient log will be kept on all head injury admissions to the study centers. If a patient is not randomized into the study, the study coordinator will record the reason. Patients will be randomly assigned to four groups as outlined above. The randomization scheme will use random permuted blocks, with blocking done for each center. Randomization will also be stratified by severity of injury (LOC 0-13 days, >14 days) to ensure an even distribution of cases. Randomization will be done centrally, and assigned by telephone in the early stages of the study. After the patient signs the informed consent and enters the evaluation program, the study coordinator should notify the study

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

statistician, who will randomize the patient and communicate the randomization results upon completion of the patient's evaluation (in order to not bias the evaluation results). A screen for case eligibility (check off boxes) will be done by each center before randomization and mailed to the USUHS Central Office. (At later stages of the study, as patient flow increases, the centers may be provided randomization envelopes with instructions.) The pharmacy at each site will dispense drug or placebo according to the pharmacy randomization log, and maintain records of drug lots received and dispensed to patients.

Treatment Programs

The details of Rehabilitation Programs A and B are outlined in the appendices. Each program will be the responsibility of a separate team of therapists, who will function independently of each other, and of the outcome evaluation personnel. Each rehabilitation program will be structured so as to be able to treat patients as they transition from lower to higher levels of cognitive function.

In order to obtain the optimum balance between treatment needs and resource allocation, each treatment module will define particular criteria for hospital discharge within a one to three month window from randomization. Patients achieving these criteria may thus be discharged to home or community transition as early as one month after randomization. Similarly, all patients will be discharged to an appropriate transitional or domiciling program closer to their home no later than three months after randomization. The mean length of hospital stay needed to reach discharge criteria may differ among the four treatment groups, and thus becomes an additional secondary outcome measure impacting on cost.

General guidelines for the rehabilitation arms are as follows (see Table 1).

1. Total hours per week in all therapies should be no less than 15, and no more than 25 (Table 1). Treatment hours actually delivered per week will be recorded by subspecialty.
2. Patients randomized to the group A (Cognitive) arm should receive about five to ten hours of basic modalities such as OT, PT, speech, minimal diversionary activities, etc., and the remainder of the time in specific cognitive interventions.
3. Patients in the functional arm should receive five to ten hours of basic modalities as well, with the remainder of time being filled in with functional activities, widely viewed as therapeutic, but which are not specific in any way to cognitive rehabilitation (e.g., recreation therapy, music therapy, etc.). These will be supervised by a recreation therapist who will provide behavioral correction and guidance in an otherwise relatively unstructured setting, with an emphasis on practical functional performance.
4. It should be strongly encouraged that therapists who are not specifically assigned to administer cognitive interventions should minimize the use of cognitive therapies, and specifically, should spend no more that about 10-20% of their session times using these kinds of approaches. This would limit the total amount of cognitive interventions in group B (Functional) to about two hours a week. Furthermore, these would be less specific and intensive. For example, patients in group B might be trained in the use of a memory book, but group A (Cognitive) would be given intensive practice in effectively utilizing this compensatory technique; or group B patients would receive redirection when they became inattentive, while group A (Cognitive) would have specific attention training modules. Likewise, speech therapy in group B will be focused specifically on aphasia treatment in aphasic patients and motor functioning, swallowing, or mouth/tongue control in dysarthric or dysphagic patients. Lists of acceptable therapies for the two rehabilitation treatment approaches will be distributed as part of standardization training for therapists.
5. In addition, all therapists in group B, and those in group A (Cognitive) who are not directly assigned to administer the specific cognitive interventions, will keep daily records of the amount and nature of all cognitive interventions they used for each patient. Sites will be monitored

Figure 2-20-M-5 Defense & Veterans Head Injury Program (DVHIP) - Protocol II (Continued)

throughout the project, and periodic retraining will be provided in order to prevent treatment drift.

TABLE I

APPROXIMATE HOURS OF THERAPY PER WEEK

	OT/PT Coping	Speech Therapy	Cognitive Therapy	Recreation Therapy	Total
Functional	5 to 12	2 to 5	0 to 2	10 to 15	15 to 25
Cognitive	5 to 12	*	10 to 15	0	15 to 25

* (embedded in cognitive program)

Transitional Management (Post Discharge)

At the completion of the inhospital treatment period, all patients will undergo an initial outcome evaluation (see below). They will then be referred to institutional or community transitional programs near their home, depending on their level of function, with specific recommendations for continued rehabilitation as indicated. Patients will return for follow-up evaluations at six, 12, and 24 months postrandomization. Recommended transitional activities for a given individual will be consistent with the program (Cognitive or SOC) to which he or she was initially randomized. A case manager at each principal site will be assigned to maintain telephonic contact with the patient at a minimum of two-week intervals, and coordinate care with the receiving veterans or military facility closest to the patient's home. Arrangements will be made for local physician follow-up. It is anticipated that at least three levels of care may be needed.

1. High level patients discharged to home may require little more than referral to a community support group and regular communication with a case manager.
2. Intermediate level patients may require more intensive outpatient or community reintegration programs centered either at a participating VAMC, or a private facility contracted through various funding mechanisms.
3. Patients who remain at a low functional level (Rancho < 6) after the inpatient program may require long-term inpatient care at a DVA, domiciling, or private facility close to their home.

While it will thus be impossible to standardize transitional management across centers as tightly as the inpatient program, an attempt will be made to minimize any variation by providing specific recommendations for management at the time of discharge and coordinating closely with the receiving facility. In addition, data will be collected specifying the type and intensity of interventions received after discharge. Transitional treatments will thus be monitored over each hospital to determine and limit any referral biases which may emerge.

STUDY MEDICATIONS

Sertraline

Sertraline or sertraline placebo will be administered in a gradually increasing dosage beginning with 25 mg daily (one-half caplet) for four days, then 50 mg daily (one caplet) for four days, then 75 mg daily for one week (one and one-half caplets), then 100 mg daily (two caplets). Should potential sertraline side effects, such as gastrointestinal upset or diarrhea, occur and persist, drug may be reduced to the previous dosage step. Drug/placebo will then be continued at the highest tolerated dosage step. Sertraline or sertraline placebo will be continued for a total of six months from randomization.